Evidence-based Practice Center Systematic Review Protocol

Project Title: Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Nosocomial Pneumonia

I. Background and Objectives for the Systematic Review

Hospital-acquired (or nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection and the leading cause of hospital-acquired infection in the intensive care unit (ICU).[1] In the ICU setting, it accounts for up to 25 percent of all infections and for more than 50 percent of the antibiotics prescribed.[1] HAP is associated with increased morbidity and mortality, length of stay, and costs of care, despite advances in antimicrobial therapy, supportive care, and prevention. Concerns about the increasing rates of superinfection (i.e., infection with a new organism) and multidrug-resistant pathogens call for ways to optimize existing antibiotic treatment for HAP. To improve the effectiveness of the available antibiotics, the 2005 American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) guidelines recommend using pharmacokinetic and pharmacodynamic (PK/PD) measures to select an antibiotic regimen, dosage, and route of administration with the goal of maximizing treatment effectiveness.

The 2005 ATS/IDSA guidelines provide the following definitions for HAP, ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP)[1]:

- HAP is a pneumonia that occurs 48 hours or more after admission and was not incubating at the time of admission. HAP may be managed in a hospital ward or in the intensive care unit (ICU) when the illness is more severe. Some patients may require intubation after developing severe HAP and should be managed similarly to patients with VAP.
- VAP is a pneumonia that presents more than 48 hours after endotracheal intubation.
- HCAP is a pneumonia that develops in any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic. Most of the principles of HAP and VAP overlap with HCAP.

Unless specified otherwise, the term "HAP" includes VAP and HCAP.

HAP is frequently caused by bacterial pathogens, which may be polymicrobial; aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and Acinetobacter species, are the most common causes of HAP. Cases of infections caused by Gram-positive cocci, including *Staphylococcus aureus*, are becoming more common in the United States. HAP caused by *S. aureus* is found with greater frequency in

patients with diabetes mellitus, patients with head trauma, and patients hospitalized in ICUs. HAP caused by viral or fungal pathogens is rare in immunocompetent patients.[1]

Patients who have received mechanical ventilation are at the greatest risk for nosocomial pneumonia; intubation increases a patient's HAP risk by 6 to 21 times. Numerous other factors may increase a patient's risk for nosocomial pneumonia[2]:

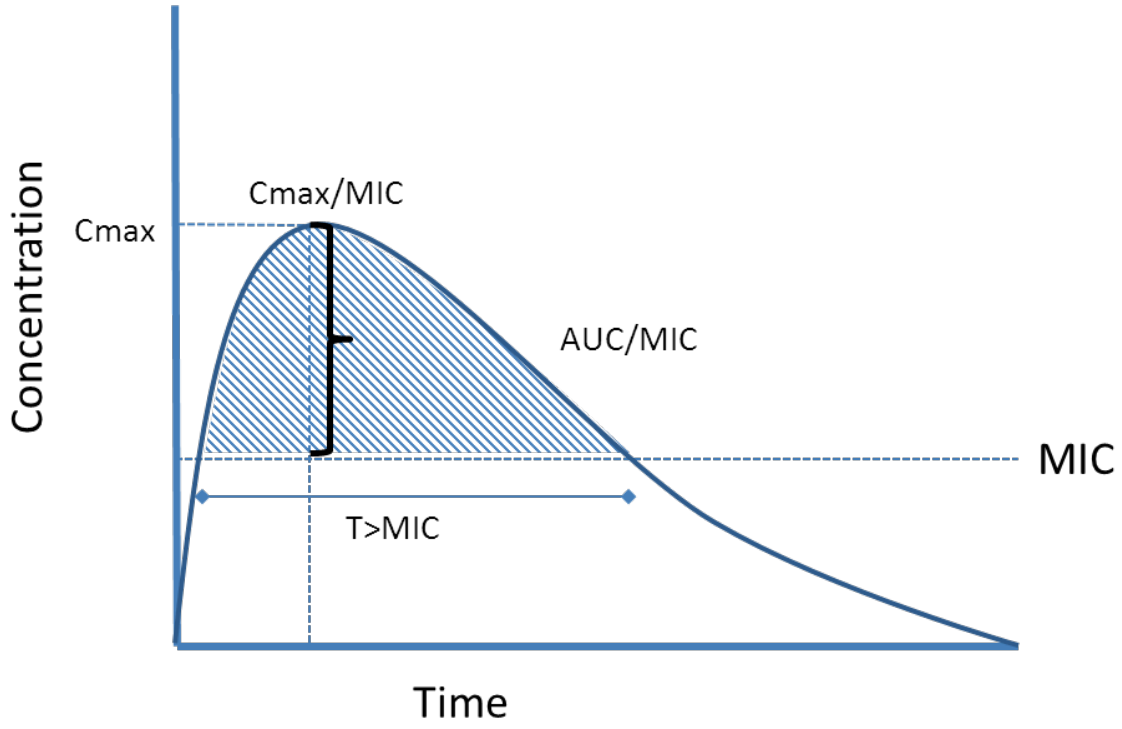
- Age >70 years
- Chronic lung disease
- Depressed consciousness
- Aspiration
- Chest surgery
- The presence of an intracranial pressure monitor or nasogastric tube
- H2 blocker or antacid therapy
- Transport from the ICU for diagnostic or therapeutic procedures
- Previous antibiotic exposure, particularly to third-generation cephalosporins
- Reintubation or prolonged intubation
- Hospitalization during the fall or winter season
- Mechanical ventilation for acute respiratory distress syndrome
- Frequent ventilator circuit changes
- Paralytic agents
- Underlying illness

Use of Pharmacokinetic and Pharmacodynamic Measures for Dosing and Monitoring of Antibiotics

Appropriate antibiotic therapy has been shown to improve survival significantly for patients with HAP.[3-6] Optimal treatment involves choosing the right drug or combination of drugs, the right dose and route of administration, and the right duration, followed by de-escalation to pathogen-directed therapy once culture results are known.[1] Subtherapeutic dosing of antibiotics has been associated with poorer clinical outcomes and increased incidences of drug resistance.[7-10] Optimal dosing of antibiotics based on PK/PD principles has the potential to improve outcomes and prevent the development of resistance in patients with HAP. PK is the study of the time course of drug absorption, distribution, metabolism, and excretion. The primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of an individual patient's drug therapy. PD refers to the relationship between the concentration of the drug at the site of action and the resulting effect. Antibiotic PD relates PK parameters to the ability of an antibiotic to kill or inhibit growth of bacterial pathogens.[11] Antibiotics can be classified based on PD characteristics that affect bacterial killing in relation to the minimal inhibitory concentration (MIC) of the organism. In general, antibiotics are grouped into one of three categories based on their mode of bacterial killing: (1) concentration dependent, (2) time dependent, or (3) a combination of concentration and time dependent. These three modes are expressed as ratios to the MIC of the organisms (Figure 1).

- Concentration-dependent antibiotic: peak concentration to MIC ratio (C_{max}/MIC)
- Time-dependent antibiotic: time the serum concentration is greater than the MIC (T>MIC)
- Area under the concentration-time curve to MIC ratio (AUC/MIC)

Figure 1. Ratios to the MIC of the organisms



Abbreviations: AUC = antibiotic area under the curve; AUC/MIC = the ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms; C_{max} = the maximum serum concentration needed to inhibit microorganisms; C_{max}/MIC = ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit microorganisms; MIC = minimal inhibitory concentration; T = time

Given the PK/PD properties of antibiotics, clinicians can optimize the PD effects of antibiotics by altering the dosing methods for the antibiotic. In order to optimize the PD effect of concentration-dependent antibiotics such as the aminoglycosides, the dose is increased, resulting in a higher C_{max}/MIC ratio. The traditional method of aminoglycoside dosing has been to divide the total daily dose into two or three equal doses. Based on PD evidence, many clinicians have adopted the practice of administering aminoglycosides using an extended-interval dosing scheme to take advantage of the concentration-dependent effects of the drug. A target of C_{max}/MIC >10 has been proposed. This target is based upon retrospective clinical data correlating clinical response with specific C_{max}/MIC targets.[12,13] To achieve this target, the total aminoglycoside daily dose is administered as a single bolus infusion over 30 to 60 minutes instead of the traditional divided doses.

For time-dependent antibiotics such as beta-lactams, strategies of prolonged or continuous infusions have been employed to optimize the T>MIC. The standard administration method for intravenous beta lactam antibiotics is intermittent bolus dosing; however, pharmacodynamic data have shown that administration of beta-lactam antibiotics by prolonged infusions produces a higher T>MIC ratio when compared with intermittent dosing. A target T>MIC of at least 50 to 70 percent of the dosing interval has been proposed based on studies in animal infection models.[14-17] The use of prolonged or continuous infusions of beta lactam antibiotics, instead of intermittent bolus dosing, should increase the percentage of time that antibiotic concentrations are above the MIC in the serum, which may correlate with efficacy, especially for organisms with high MICs. While these strategies may offer a pharmacodynamic advantage, studies evaluating the clinical outcomes of these approaches have shown conflicting results.[18-20]

For antibiotics in which the AUC/MIC ratio is the predictor of efficacy, such as vancomycin, concentration monitoring to achieve a specific AUC/MIC target can be used to optimize dosing. Vancomycin monitoring guidelines were published in 2009 by the Society of Infectious Diseases Pharmacists, the American Society of Hospital Pharmacists, and the IDSA. These guidelines recommend a target AUC/MIC ratio of 400 for optimal efficacy of vancomycin. Because serum trough concentration monitoring is more practical than AUC monitoring in clinical settings, a goal trough concentration of 15–20 mg/L is recommended for the treatment of HAP caused by methicillin-resistant *S. aureus* with an MIC ≤1 mg/L. For organisms with an MIC >1 mg/L, the target AUC/MIC of 400 becomes more difficult with standard dosing. The recommendations from this guideline were based on PK analyses and retrospective, observational studies.[21] The clinical benefit of various vancomycin targets remains a subject of controversy.

Pharmacodynamic targets become more difficult to achieve as the MIC for an organism increases. As the prevalence of antibiotic-resistant bacteria continues to rise, particularly among the critically ill, choosing the optimal antibiotic dosing regimen is important to increase the likelihood of clinical success. The optimal dosing regimen will achieve the appropriate PD target without increasing the risk of concentration-related toxicities. For drugs with a narrow therapeutic index, such as vancomycin and the aminoglycosides, the risk of toxicities is often a dose-limiting factor.

The probability of attaining the PD target not only changes with the organism MIC but also with variations in patient-specific factors. The efficacy of an antibiotic depends on its ability to reach the site of infection in sufficient concentrations to inhibit bacterial activity.[22] Optimizing PK/PD can increase the likelihood of obtaining adequate concentrations of the appropriate drug and enhancing outcomes for patients with HAP. In critically ill patients, however, alterations in fluid distribution, homeostasis, hemodynamic state, microcirculation, and organ function are common. These factors are essential to understanding and choosing an effective therapeutic regimen, and they can affect PK and PD properties.[22,23] A recent multicenter study demonstrated significant variability in antibiotic trough concentrations in critically ill patients receiving continuous renal replacement therapy that the intensity of the therapy did not predict; this observation suggested that desirable clinical results cannot reliably be achieved with empiric dosing.[24] Current recommended dosing strategies that are based on animal or in vitro models or on data from noncritically ill patients may not account for these factors, placing these patients at risk of treatment failure, adverse effects from drug toxicity, antibiotic resistance, and death.

In their consensus document on controversial issues for the treatment of hospital-associated pneumonia, Franzetti et al.[25] recommended using PK/PD parameters, particularly monitoring of the trough serum concentration of vancomycin, in treating critically ill patients with HAP. They based their guidance on evidence that optimizing PK/PD parameters may prevent treatment failure and resistance; it may also reduce nephrotoxicity in patients who are receiving aggressive dosing, concurrent nephrotoxic drugs, or prolonged courses of therapy and or in patients with unstable renal function.

Existing Guidance

The 2005 ATS/IDSA guidelines recommend using PK/PD measures for selecting an antibiotic regimen, dosage, and route of administration with the goal of maximizing treatment effectiveness to improve the efficacy of available antibiotics. However, they acknowledge that the impact of PK/PD measures on improving clinical outcomes and survival in people with HAP has yet to be determined. Most empiric antibiotic-dosing regimens are based on data from noncritically ill patients (with or without renal impairment). Critically ill patients frequently face alterations in organ function, homeostasis, and hemodynamics that may influence PK/PD parameters and bacterial susceptibility, which may render some dosing recommendations inadequate. Updating existing evidence-based guidelines with new data derived from patients with HAP, including those who are critically ill with or without renal impairment, may help improve antibiotic use and associated clinical outcomes and reduce antibiotic resistance.

Rationale for the Evidence Review

This topic has a high degree of potential impact. Determining the most effective regimen for dosing and administration of initial empiric antibiotic therapy may accomplish many goals, such as to reduce the morbidity and mortality associated with suboptimal antibiotic therapy, improve clinical response, and decrease adverse events for patients with HAP, which may result in lower health care costs. Although existing guidance recommends using PK/PD measures to guide the treatment of individuals with nosocomial pneumonia, previous reviews have not determined the impact of using these measures on the outcomes outlined above.

A new systematic review on this topic would not duplicate existing reviews. A feasibility scan of MEDLINE®, EMBASE®, the Cochrane Library, Agency for Healthcare Research and Quality evidence reports, and the HTA (Health Technology Assessment) database identified two systematic reviews that evaluated a correlation between PK/PD and microbiologic or clinical outcomes in patients with HAP. The review by Franzetti and colleagues[25] (undertaken on behalf of the Italian Study Group on Serious Infections) focused narrowly on treatment (primarily vancomycin) for only Gram-positive pathogens. Of the seven studies included in the final analysis, only three retrospective cohorts (published between 2004 and 2007) included HAP; of these, two involved the same patient group with HCAP caused by methicillin-resistant *S. aureus*. These studies were limited by a small sample size and retrospective design, and none evaluated mortality as an outcome. The second review by Abdul-Aziz and colleagues,[26] which was not limited to patients with HAP, included only one study[27] that compared intermittent dosing versus continuous infusion of beta-lactam antibiotics in patients with VAP and found no significant differences in the clinical outcomes (i.e., duration of mechanical ventilation, length of stay, and

fever resolution). Abdul-Aziz and colleagues[26] did not appraise the quality of individual studies or grade the quality of the evidence, and their review was narrowly focused on one drug class—namely, beta-lactam antibiotics. The available evidence identified by the preliminary literature scan encompasses a broader range of antibiotics for treating both Gram-positive and Gram-negative pathogens. A comprehensive systematic review at this time would include a broader range of antibiotics and pathogens than the previously identified reviews; examine additional outcomes of interest not covered in previous reviews; and inform clinical decisionmaking for patients, clinicians, health systems, and payers.

This review will not address aerosolized antibiotics and antifungals because PK/PD measures are not used to guide treatment with these drugs.

II. The Key Questions

Summary of Revisions to the Key Questions

The Key Questions (KQs) were available for public comment from March 22 through April 18, 2013. Based on public comments, we have added renal dysfunction as a subgroup in KQ 3. Based on comments from the Agency for Healthcare Research and Quality (AHRQ) regarding the clarity of the analytic framework, the outcomes of the KQ were revised to be nondirectional rather than designated only as a benefit or harm. During discussions with the Technical Expert Panel (TEP), some concerns were expressed about the possibility that dose-monitoring studies, in which PK/PD principles are used to determine dosing but no therapeutic drug monitoring occurs during the study, would be excluded based on the KQs. Following this discussion, a new KQ was added to examine the effect of using prolonged or continuous infusions of drugs on outcomes. The KQs were then rearranged for clarity of construction, and mechanical ventilation was added to KQs 1 and 2 to more accurately reflect the outcomes listed in the PICOTS (**p**opulation, **i**ntervention, **c**omparator, **o**utcomes, **t**iming, and **s**etting) and analytic framework.

Question 1

For people with nosocomial pneumonia, how does using PK/PD measures to inform decisions about dosing or monitoring antibiotic treatment impact:

a. Clinical response or mechanical ventilation?
b. Morbidity or mortality?
c. Rates of antibiotic-related adverse events?

Question 2

For people with nosocomial pneumonia, how does using prolonged or continuous infusions compare with bolus infusions for beta-lactams impact:

a. Clinical response or mechanical ventilation?
b. Morbidity or mortality?

c. Rates of antibiotic-related adverse events?

Question 3

Does the evidence for morbidity, mortality, antibiotic-related adverse events, clinical response, and mechanical ventilation differ for subgroups defined by age, sex, race, ethnicity, renal dysfunction/need for dialysis, severity of illness, micro-organism, or susceptibility patterns?

Our review addresses the same PICOTS for all of the KQs, except for the harms outcomes, as described below.

- **Population(s):**
  - Adults who have presumed or confirmed HAP, VAP, or HCAP and who are being treated with intravenous antibiotic treatment.
- **Interventions:**
  - KQ 1 and KQ 3: Use of PK/PD measures for dosing and monitoring intravenous antibiotics: serum concentration, volume of distribution, protein binding, creatinine clearance, time above MIC, and ratio of AUC to MIC (see Table 1 below for drug classes and drugs of relevance)
  - KQ 2 and KQ 3: Prolonged or continuous infusion
- **Comparators:**
  - KQ 1 and 3
    - No use of PK/PD measures
    - Different targets of PK/PD measures
    - Usual care (e.g., physician discretion or judgment, local epidemiology of bacteria and resistance)
  - KQ 2 and KQ 3
    - Bolus dosing
- **Outcomes for each question:**
  - KQ 1a, KQ 2a, and KQ 3: Intermediate outcomes
    - Clinical response
    - Mechanical ventilation (occurrence or length)

- KQ 1b, KQ 2b, and KQ 3: Health outcomes
  - Mortality
    - In hospital
    - Within 30 days of discharge
    - All-cause mortality
    - Mortality due to pneumonia
  - Morbidity
    - Reinfection, or two episodes of pneumonia with different pathogens
    - Relapse, or second episode of pneumonia with the same pathogen
    - Superinfection, or infection with multiple pathogens

- KQ 1c, KQ 2c, and KQ 3: Antibiotic-related adverse events
  - Organ toxicity (e.g., hepatotoxicity, nephrotoxicity)
  - Hematologic effects (e.g., anemia, thrombocytopenia)
  - *Clostridium difficile* infection
  - Antibiotic resistance (reported at either the patient or unit level)

- **Timing:**
  - No limitations

- **Settings:**
  - Treatment beginning in the hospital (emergency department, floor, or ICU). Treatment that continues in other settings will be included.

Table 1. Antibiotics for which PK/PD measures could be used

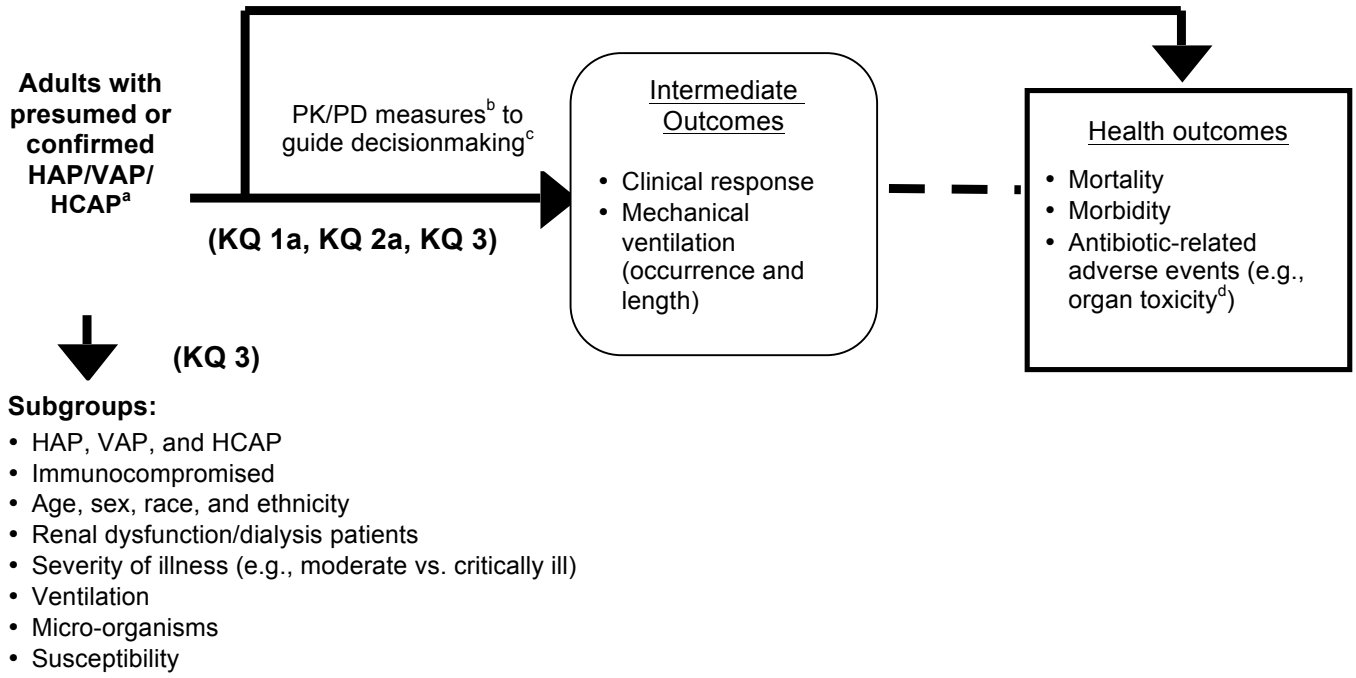
Drug Class	Drug Group	Drug*
Aminoglycosides		**Gentamicin** **Tobramycin** **Amikacin**
Beta-lactams	Penicillins	Penicillin G Oxacillin Nafcillin
	Beta-lactam Beta-lactamase inhibitors	Ampicillin/sulbactam **Piperacillin/tazobactam** **Ticarcillin/clavulanic acid**
	Cephalosporins	Cefazolin Ceftriaxone Cefotaxime **Ceftazidime** **Cefepime** Ceftaroline
	Monobactams	**Aztreonam**
	Carbapenems	**Doripenem** Ertapenem **Imipenem** **Meropenem**

Fluoroquinolones	NA	Levofloxacin Ciprofloxacin Moxifloxacin
Glycopeptides	**NA**	**Vancomycin**
Glycylcyclines	Cyclins	Tigecycline
Oxazolidinone	**NA**	**Linezolid**
Polymyxin	NA	Colistin (also called colistimethate sodium)
Rifamycins	Rifamycins	Rifampin Rifampicin
Tetracyclines	Tetracyclines	Doxycycline Minocycline

*Drug names in boldface represent those intravenous antibiotics most commonly used to treat nosocomial pneumonia.
Abbreviations: NA = not applicable; PK/PD = pharmacokinetic and pharmacodynamic

III. Analytic Framework

Figure 2. Analytic framework for use of pharmacokinetic/pharmacodynamic measures to guide antibiotic treatment for nosocomial pneumonia



[a] Does not include patients with community-acquired pneumonia but does include patients with nursing home–acquired pneumonia.
[b] These measures are serum concentration, volume of distribution, MIC, ratio of AUC to MIC, and protein binding.
[c] Decisionmaking involves dosing or monitoring of treatment.
[d] The types of organ toxicity are nephrotoxicity, ototoxicity, neurotoxicity, et cetera.

Abbreviations: AUC = antibiotic area under the curve; CPIS = Clinical Pulmonary Infection Score; HAP = hospital-acquired pneumonia; HCAP = health care–associated pneumonia; MIC = minimum inhibitory concentration; PD = pharmacodynamic; PK = pharmacokinetic; VAP = ventilator-associated pneumonia

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The following table summarizes the inclusion and exclusion criteria that will be applied to studies evaluated for the systematic review.

Table 2. Criteria for inclusion/exclusion of studies in the review

PICOTS Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adults (age 18 years or older) who have presumed or confirmed HAP, VAP, or HCAP and are being treated with intravenous antibiotics (listed in Table 1)	• Children and adolescents under 18 years of age • Fungal pneumonia • Other methods of administration (i.e., inhaled antibiotics)
Geography	No limits	
Time period	No date limit; searches to be updated after the draft report goes out for peer review	
Length of followup	No limits	
Settings	• Treatment beginning in the hospital (emergency department, floor, or ICU) • Treatment continuing in other settings (e.g., in the home or in a skilled nursing facility) • Pneumonia developing in the hospital	Treatment beginning in other settings, such as nursing homes
Interventions	• KQ 1 and KQ 3: Use of PK/PD measures for dosing and monitoring intravenous antibiotics: ○ Serum concentration ○ Volume of distribution ○ Protein binding ○ Time above MIC ○ Ratio of AUC to MIC • KQ 2 and KQ 3: Prolonged or continuous infusion	
Comparators	• KQ 1 and KQ 3: ○ No use of PK/PD measures ○ Different targets of PK/PD measures ○ Usual care (e.g., physician discretion or judgment, local epidemiology of bacteria and resistance) • KQ 2 and KQ 3: Bolus dosing	• No comparator • Studies in which only serum concentration is measured, without targeting different serum concentration levels

Table 2. Criteria for inclusion/exclusion of studies in the review (continued)

PICOTS Criteria	Inclusion Criteria	Exclusion Criteria
Outcomes	• KQ 1a, KQ 2a, and KQ 3 ○ Intermediate: ▪ Clinical response ▪ Mechanical ventilation (occurrence or length) • KQ 1b, KQ 2b, and KQ 3 ○ Mortality ▪ In hospital ▪ Within 30 days of discharge ▪ All-cause mortality ▪ Mortality due to pneumonia • KQ 1b, KQ 2b, and KQ 3 ○ Morbidity ▪ Reinfection, or two episodes of pneumonia with different pathogens ▪ Relapse, or second episode of pneumonia with the same pathogen ▪ Superinfection, or infection with multiple pathogens • KQ 1c, KQ 2c, and KQ 3 ○ Antibiotic-related adverse events ▪ Organ toxicity (e.g., hepatotoxicity, nephrotoxicity) ▪ Hematologic effects (e.g., anemia, thrombocytopenia) ▪ *Clostridium difficile* infection ▪ Antibiotic resistance (reported at either the patient or unit level)	No outcomes of interest
Publication language	English	All other languages[a]
Admissible evidence (study design and other criteria)	Original research; eligible study designs include: • **For all KQs:** randomized controlled trials with masking of subjects and providers (i.e., double-blind), nonrandomized controlled trials, or prospective cohort studies with an eligible comparison group • **For KQ 1c, KQ 2c, and KQ 3:** adverse events, case-control studies and retrospective cohorts will also be included	• Nonsystematic reviews • Systematic reviews • Editorials • Letters to the editor • Articles rated as having high risk of bias • Case reports • Case series • Studies with historical, rather than concurrent, control groups

[a]Due to limited time and resources, we will only include studies published in English.

Abbreviations: AUC = antibiotic area under the curve; HAP = hospital-acquired pneumonia; HCAP = health care–associated pneumonia; ICU = intensive care unit; KQ = key question; MIC = minimum inhibitory concentration; PD = pharmacodynamic; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PK = pharmacokinetic; VAP = ventilator-associated pneumonia

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions –

To identify articles relevant to each KQ, we will begin with a focused MEDLINE® search on nosocomial pneumonia, pharmacokinetics or pharmacodynamics, and antibiotics by using a variety of terms, medical subject headings (MeSH®), and major headings and limiting our search to only English-language and human studies. Relevant terms are listed in Table 3. We will also search the Cochrane Library and International Pharmaceutical Abstracts (IPA) by using analogous search terms. We will conduct quality checks to ensure that the known studies (i.e., studies identified during topic nomination and refinement) are identified by the search. If they are not, we will revise and rerun our searches.

Table 3. Literature search terms

Populations	(Pneumonia Type Terms AND Pneumonia Terms) OR (Terms for HAP, VAP, or HCAP)
Pharmacokinetics	(Terms for Pharmacokinetic* OR AUC OR Bioavailability OR Metabolic Clearance OR Therapeutic Equivalency OR Absorption OR Distribution OR Metabolism OR Excretion OR Protein Binding OR Therapeutic Index OR Trough OR Peak OR Therapeutic Drug Monitoring)
Pharmacodynamics	(Terms for Pharmacodynamic* OR Toxicity OR Drug-related Adverse Events OR Dose-Response Relationship OR MIC OR AUC OR Microbial Sensitivity OR Time Kill Curve)
Antibiotics	(Terms for drugs listed in Table 1) OR ("anti-bacterial agent*"[all fields] OR "antibiotic*"[all fields] OR "Anti-Bacterial Agents"[mesh])
Limits	Humans English language Adults 19+ years or Adults 18+ years **NOT the following:** Editorial, Letter, Addresses, Autobiography, Bibliography, Biography, comment, Congresses, Consensus Development Conference, NIH, Dictionary, Directory, Festschrift, Interactive Tutorial, Interview, Lectures, Legal Cases, Legislation, Patient Education, Handout, Periodical Index, Portraits, Scientific Integrity Review, Video-Audio Media, Webcasts

As no previous reviews or guidelines closely matched the scope and methodology of this review, the searches will not be limited by date.

We will search the "gray literature" for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessment of internal validity/quality. Gray literature sources will include ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, and scientific information packets, which the Scientific Resource Center will request from pharmaceutical and test manufacturing companies.

Our search strategy was reviewed by the TEP for feedback. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background

articles on this topic to look for any relevant citations that might have been missed by our electronic searches.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by Peer Reviewers or public comment respondents will be investigated and, if found appropriate, incorporated into the final review. Appropriateness will be determined by the same methods listed above.

C. Data Abstraction and Data Management

All titles and abstracts identified through our searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® (Thomson Reuters, New York, NY) database.

We will retrieve and review the full text of all articles identified for possible inclusion during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the research team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet the inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will abstract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team.

D. Assessment of Methodological Risk of Bias of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we will use predefined criteria based on the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[28] including questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias (i.e., those about adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity). In general terms, results from a study assessed as having low risk of bias are considered to be valid. A study with moderate risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as having high risk of bias has significant risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) that may

invalidate its results. We plan to omit studies deemed to have high risk of bias from our main data synthesis and main analyses; we will include them only in sensitivity analyses.

Two independent reviewers will assess risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

E. Data Synthesis

Prioritization and/or categorization of outcomes will be determined by the research team with input from TEP members. If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. In order to determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.[29] We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. When appropriate, studies will be combined by using a random-effects model while accounting for variation among studies.[30] We will assess the presence of statistical heterogeneity among studies by using standard χ^2 tests and the magnitude of heterogeneity by using the I^2 statistic.[31,32] Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework. When quantitative syntheses are not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, insufficiency of outcome reporting or variation in outcome reporting), we will synthesize the data qualitatively.

If sufficient data are available, meta-analyses and results will be stratified by (1) method of PK/PD measure, (2) Gram-positive or Gram-negative pathogen, and finally (3) drug class.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center (EPC) Program.[33] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as dose-response association, plausible confounding that would decrease the observed effect, strength of association (i.e., magnitude of effect), and publication bias.

Table 4 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus.

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect; further research is very unlikely to change our confidence in the estimate of effect.

Moderate	Moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al.[33]

We will grade the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers, Key Informants, and the TEP members.

G. Assessing Applicability

We will assess the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[34] For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Such conditions may be associated with heterogeneity of treatment effect, measurement of absolute (rather than relative) benefits and harms, and the ability to generalize the effectiveness of an intervention to use in everyday practice. Some factors identified a priori that may limit the applicability of evidence include the following: severity of illness, chronic lung disease, heterogeneous population/population not well defined, and setting.

V. References

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VI. Definition of Terms

AUC over the MIC. Ratio of the antibiotic area under the curve (AUC) to the time above the minimum inhibitory concentration (MIC) needed to inhibit micro-organisms.

C_{max}/MIC. Ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit micro-organisms.

Hospital-acquired pneumonia (HAP). Pneumonia that occurs 48 hours or more after admission (not incubating at the time of admission). In this brief, HAP includes health care–associated pneumonia (HCAP) and ventilator-acquired pneumonia (VAP).

Health care–associated pneumonia (HCAP). Includes pneumonia in any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.

Multidrug-resistant pathogens. Pathogens that have resistance to at least two or more of the antibiotics commonly used to treat them.

Minimal inhibitory concentration (MIC). The minimum concentration of an antibiotic needed to inhibit micro-organisms.

Pharmacokinetic/pharmacodynamic (PK/PD) measures. These measures include serum concentration, volume of distribution, MIC, and the ratio of AUC to MIC.

Ventilator-acquired pneumonia (VAP). Pneumonia that presents more than 48 hours after endotracheal intubation.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all Evidence-based Practice Center (EPC) reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons,

or outcomes, as well as in identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence Report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators. The EPC core team has no conflicts to disclose.

XIII. Role of the Funder

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The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.